REMARKS

Withdrawal of the final rejection, entry of the above amendments and favorable reconsideration of this application is requested.

The claims are amended to address the objections and rejections, thereby placing the application in condition for allowance, without raising new issues requiring further consideration or search and without raising issues of new matter.

Specifically, Claim 1 and dependent claims, are amended to replace references to "tagged" and "untagged" molecules with "exogeneously administered polypeptide" and "endogenous polypeptide" respectively. Correspondingly, in claim 1, the phrase "is tagged with" is changed to "has" to provide consistency throughout the claims.

Other minor changes have also been made in response to the claim objections. Specifically, in claims 3 and 5, the appropriate corrections suggested by the Examiner have been made, and in claim 27, the amendment provides the appropriate antecedent basis.

The deletion of "tagged" and "untagged" by the amendment to claim 1 obviates the bases for the Section 112, first and second paragraph rejections. However, it is respectfully submitted that the rejections were improper.

As understood, the basis for these rejections is the unfounded assumption or characterization that "the selected fluorescent wavelength is due only to the presence of the tag" (emphasis supplied). This is not what is disclosed or claimed. What was stated in claim 1 is that, "the greater or lesser amount of fluorescence activity is due to the respective presence or absence in the tagged molecule, relative to the untagged molecule, of a fluorescent amino acid residue ..." Nowhere is it

stated or implied that tagging is responsible for all of the fluorescence activity at a particular wavelength. It is the difference in fluorescence activity, at the selected wavelength, which is provided by "tagging" the exogenously administered polypeptide. The present claims still define this feature by reciting that the fluorescent amino acid residue or synthetic amino acid derivative is present in or absent from the exogenously administered polypeptide.

Apparently, the Examiner questions how the absence "tag" would allow the requisite "determination." In this regard, the Examiner is referred to, for example, the explanation given on page 5 of the specification. On page 5, second full paragraph, it is explained that the tagged molecule "is either deficient in, or comprises additional, fluorescent entities (fluorophores) relative to the untagged molecule. The tagging may be 'positive' (in whch the tagged molecule comprises additional fluorophores) or 'negative' (where the tagged molecule is deficient in fluorophores relative to the untagged molecule)."

Further explanation is given in the following paragraph, where it is explained that, for example, "if an 'untagged' polypeptide comprises one or more tryptophan and/or tyrosine residues it may be fluorescent. Thus, a tagged molecule, in accordance with the invention, may be distinguishable from an untagged molecule by having additional fluorophores ... [or] ... the tagged molecule may be distinguishable by having fewer fluorophores than the untagged molecule."

That is, "negative" tagging of an exogenous molecule may be regarded as equivalent to the "positive" tagging of the endogenous molecule, either case resulting in a differential in fluorescence activity between the two molecules.

Accordingly, Applicants respectfully disagree that the scenarios proposed by the Examiner are impossible to achieve. The premise of "impossibility" is incorrect since, contrary to the statement that "it is impossible therefore for the endogenous polypeptide to produce any fluorescent signal, much less produce a signal that has an intensity greater than that of the tagged, exogenously administered polypeptide" the specification teaches how this result can occur. Again, please see the specification, for example, page 6, lines 3-6.

Therefore, the rejections of claims 1-12 and 27, under the first and second paragraphs of 35 USC 112, as set forth in ¶¶3 and 6, are respectfully traversed.

Regarding ¶7, Applicants respectfully disagree that the specification would not be enabling in view of the disclosure of Kilhoffer et al.

As stated by the Examiner, Kilhoffer et al identified changes in fluorescence intensity of calmodulin, reflecting changes in structure of the protein upon binding of calcium ions. This disclosure does not, however, implicate any deficiency in the disclosure of the present application.

The specification provides ample description that the detection of the exogenously administered polypeptide arises as a result of the detection of a greater or lesser amount of fluorescence activity relative to that displayed by the endogenous polypeptide. Nothing more is required.

The Examiner is further requested to consider that,

(a) The results of Kilhoffer et al relate solely to calmodulin mutants comprising an additional tryptophan residue. Kilhoffer et al do not present data or evidence or even speculation relating to naturally occurring endogenous calmodulin. Therefore, any variation of the intensity of fluorescence of the tryptophan-containing mutant

forms of calmodulin with calcium ion concentration is not seen as having any bearing on the fluorescence activity of naturally occurring calmodulin in the presence of varying concentrations of calcium ion.

(b) In any event, the absolute nature of the fluorescent activity is not at issue. All that is required for operation of the method of detection is that there is a difference between the fluorescence of the endogenous and exogenous molecules. The only way for the difference to be non-existent is if the number and environment of the fluorophores is identical. Since the claims are concerned with analysis at a suitable wavelength, unless the molecules have identical fluorescence spectra, there will always be a suitable wavelength which a person of ordinary skill in the art can use in the analysis to distinguish between the endogenous and exogenous polypeptides.

(c) Even if binding of a ligand becomes a problem, which, as explained above, is extremely unlikely, the practitioner would, without any undue experimentation, easily adopt any one of numerous procedures to avoid the problem, e.g., by treating the sample with a competitor substance to compete for binding to the ligand, and then removing the competitor, (e.g., by affinity purification).

For all of the above reasons, it is respectfully submitted that the rejection for lack of enablement should be withdrawn.

Since the claims are free of the prior art and in compliance with all other statutory requirements, passage of the application to issue is earnestly solicited.

Respectfully submitted,

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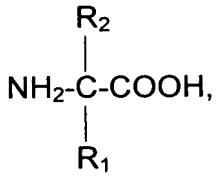
APPENDIX: Version with Markings to Show Changes Made

IN THE CLAIMS

1. (Twice Amended) A method of detecting the presence in a sample of a polypeptide exogenously administered to a mammalian subject from whom the sample is obtained, and distinguishing between such an exogenously administered polypeptide and a naturally-occurring endogenous polypeptide present in the sample; the method comprising obtaining a sample from the subject; and subjecting the sample to analysis of fluorescence at a suitable wavelength; wherein the exogenously administered polypeptide [is tagged with] has a greater or lesser amount of fluorescence activity, relative to the [untagged] endogenous polypeptide, at the wavelength(s) analysed, wherein the greater or lesser amount of fluorescence activity is due to the respective presence or absence in the [tagged molecule] exogenously administered polypeptide, relative to the [untagged molecule] endogenous polypeptide, of a fluorescent amino acid residue or a synthetic amino acid derivative, in the amino acid backbone of the polypeptide, the synthetic amino acid derivative having the formula



wherein R_1 comprises the fluorophore and R_2 is H, OH, halide or substituted or unsubstituted lower alkyl.

3. (Twice Amended) A method according to claim 1, wherein the sample is subjected to processing, prior to analysis, by one or more of the following: centrifugation; HPLC; FPLC; affinity chromatography; immunoaffinity chromatography; denaturation; or heat treatment.

5. (Twice Amended) A method according to claim 1, wherein the sample comprises one or more of the following: blood; saliva; urine; semen; or tears.

6. (Twice Amended) A method according to claim 1, wherein the [tagged molecule] exogenously administered polypeptide has greater fluorescence activity, at the wavelength analysed, than the [untagged molecule] endogenous polypeptide.

7. (Twice Amended) A method according to claim 1, wherein the [tagged molecule] exogenously administered polypeptide comprises one or more fluorophores not present in the [untagged molecule] endogenous polypeptide.

8. (Twice Amended) A method according to claim 7, wherein a compound comprising a tagging fluorophore is incorporated in the [tagged molecule] exogenously administered polypeptide by means of a peptide bond.

10. (Twice Amended) A method according to claim 1, wherein the [tagged molecule] exogenously administered polypeptide comprises a tagged therapeutic polypeptide and/or tagged hormone.

11. (Twice Amended) A method according to claim 1, wherein the [tagged molecule] exogenously administered polypeptide comprises one of the following: a tagged human, bovine or porcine growth hormone; tagged calcitonin; tagged erythropoietin; tagged growth hormone releasing factor; tagged insulin; or tagged interleukin-2.

12. (Twice Amended) A method according to claim 1, wherein the [tagged molecule] exogenously administered polypeptide comprises growth hormone tagged with a tryptophan residue at one or more postions 10, 31, 97, 160 or 176.

27. (Amended) A method according to claim 1, wherein the [tagged molecule] endogenously administered polypeptide comprises [the] a substitution, relative to the [untagged molecule] endogenous polypeptide, of one or more phenylalanine or tyrosine residues with a corresponding number of tryptophan residues.